

WHAT IS CLAIMED IS:

1. A preparation of undifferentiated embryonic stem (ES) cells maintained in an undifferentiated state and wherein said cells will undergo stem cell renewal or somatic differentiation.

2. The preparation according to claim 1 wherein said undifferentiated ES cells will differentiate into a somatic lineage upon introduction of a differentiating signal.

3. A method of culturing undifferentiated ES cells, said method including: obtaining a source of undifferentiated ES cells; and culturing the ES cells in the presence of an indirect or direct antagonist of a BMP-mediated default pathway of extraembryonic endoderm differentiation.

4. A method of producing a progenitor cell from an ES cell, said method comprising: obtaining a source of undifferentiated ES cells; and culturing the ES cells in the presence of an antagonist of a BMP mediated default pathway of extra embryonic endoderm differentiation for a period sufficient to differentiate the ES cell to a progenitor cell.

5. The method according to claim 3 wherein the source of undifferentiated ES cells is selected from the group including an embryo, a blastocyst, or a culture of undifferentiated orientated stem cells.

6. The method according to claim 5 wherein the ES cells are cultured in the presence of an indirect or direct antagonist of a BMP-2 mediated default pathway of extraembryonic endoderm differentiation.

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7. The method according to claim 6 wherein the antagonist is a direct antagonist of the BMP-2 mediated default pathway selected from the group consisting of fetuin, noggin, chordin, gremlin, follistatin, cerberus, amnionless, DAN, or the ectodomain of BMPRII (a BMP receptor protein) or ligand binding domains from other BMP receptors.

8. The method according to claim 7 wherein the antagonist comprises a domain of noggin.

9. The method according to claim 8 wherein the antagonist is a human or mouse noggin.

10. The method according to claim 8 wherein the noggin is a mouse BMP antagonist noggin comprising amino acid residues 20 to 232 of mouse noggin.

11. The method according to claim 8 wherein the noggin is in the range of 100 to 500 ng/ml.

12. The method according to any one of claims 4-10 wherein the period sufficient to differentiate the ES cell to a progenitor cell is at least 5 days and the noggin is in the range of 100 to 500 ng/ml.

13. An undifferentiated ES cell prepared by a method according to claim 3.

14. A progenitor cell prepared by the method according to claim 4.

15. The undifferentiated ES cell or a progenitor cell according to any one of claims 1, 13 or 14 characterised by being unreactive with any one of the antibodies including PHM4 recognising MHC Class 1 surface molecules, anti-desmin, UJ13A reactive with polysialylated N-CAM, Cam 5.2 reactive with low

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molecular weight cytokeratins, AMF reactive with vimentin intermediate filaments, antibody to 160 kDa neurofilament protein, GCTM-2 reactive with a proteoglycan present on the surface of ES cells, TG42.1 reactive with a 25 kDa protein which copurifies with the proteoglycan recognised by GCTM-2 and is found on stem cells and other cell types, monoclonal antibody GCTM-5 reactive with an unknown molecule present on a small proportion of cells in spontaneously differentiating human EC cell cultures,.

16. The method according to claim 6 wherein the antagonist is an indirect antagonist of the BMP-2 mediated default pathway selected from the group consisting of insulin, insulin analogue, or a cell derived insulin or insulin analogue-induced-factor.

17. The method according to claim 16 said method including:
obtaining a source of undifferentiated ES cells; and
culturing the ES cells in the presence of insulin or an insulin analogue.

18. The method according to claim 17 further including culturing the embryonic stem cells in the presence of a fibroblast feeder layer.

19. The method according to claim 18 including the steps of:
obtaining a source of undifferentiated ES cells;
culturing the ES cells on a fibroblast feeder cell layer; and
subjecting the cultured ES cells on the fibroblast feeder cell layer to an effective amount of insulin or an insulin analogue.

20. The method according to claim 17 wherein the insulin or insulin analogue is present in the range of 10ng/ml to 10µg/ml.

21. The method according to claim 16, said method including:

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obtaining a source of undifferentiated ES cells; and
 culturing the ES cells in the presence of a cell derived insulin or insulin
 analogue induced factor.

5 22. The method according to claim 21 wherein the cell derived insulin or insulin
 analogue induced factor is derived from conditioned medium of another culture of
 ES cells exposed to insulin or insulin analogue.

23. The method according to claim 22 wherein the other culture of ES cells is
 10 exposed to insulin in the range of 10ng/ml to 10µg/ml.

24. An undifferentiated ES cell or a progenitor cell prepared by the method
 according to any one of claims 16 to 23.

15 25. A method of culturing undifferentiated ES cells, said method including:
 obtaining a source of undifferentiated ES cells; and
 culturing the ES cells in the presence of an indirect and direct antagonist of
 a BMP-mediated default pathway of extraembryonic endoderm differentiation.

20 26. The method according to claim 25 wherein the BMP mediated default
 pathway is a BMP-2 mediated default pathway.

27. The method according to claim 25 wherein the culturing of the ES cell in the
 presence of the direct antagonist of the BMP-2 mediated default pathway selected
 25 from the group consisting of fetuin, noggin, chordin, gremlin, follistatin, cerberus,
 amnionless, DAN, or the ectodomain of BMPR1A (a BMP receptor protein) or
 ligand binding domains from other BMP receptors.

28. The method according to claim 25 wherein the culturing of the ES cell in the
 30 presence of the indirect antagonist of the BMP-2 mediated default pathway

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selected from the group consisting of insulin, insulin analogue, or a cell derived insulin or insulin analogue-induced-factor.

29. An undifferentiated ES cell or a progenitor cell prepared by the method
5 according to any one of claims 25 to 28.

30. A method of producing a somatic cell from an undifferentiated ES cell, said method including:

obtaining a progenitor cell comprising obtaining a source of undifferentiated
10 ES cells;

culturing the ES cells in the presence of an antagonist of a BMP mediated default pathway of extra embryonic endoderm differentiation for a period sufficient to differentiate the ES cell to a progenitor cell;

obtaining a progenitor culture medium;
15 culturing the progenitor cell in the progenitor culture medium; and
obtaining a somatic cell from a lineage of the progenitor.

31. The method according to claim 30 wherein the progenitor culture medium is derived from a culture of neural progenitors which can differentiate into neural or
20 glial cells.

32. A somatic cell prepared by the method according to claim 30.

33. A neural cell prepared by the method according to claim 31
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34. A method according to claim 30 wherein the ES cells are cultured in the absence of a feeder cell layer.

35. A glial cell prepared by the method according to claim 34.
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36. A cell derived insulin or insulin analogue induced factor capable of maintaining ES cells in an undifferentiated state but capable of differentiation into a somatic lineage said factor derived from ES cells exposed to insulin or insulin analogue.

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37. The factor according to claim 36 wherein the insulin or insulin analogue is exposed to the ES cells in the range of 10ng/ml to 10µg/ml for a period of at least 5 days.

10 38. The method according to claim 4 wherein the source of undifferentiated ES cells is selected from the group including an embryo, a blastocyst, or a culture of undifferentiated orientated stem cells.

15 39. The method according to claim 38 wherein the ES cells are cultured in the presence of an indirect or direct antagonist of a BMP-2 mediated default pathway of extraembryonic endoderm differentiation.

20 40. The method according to claim 39 wherein the antagonist is a direct antagonist of the BMP-2 mediated default pathway selected from the group consisting of fetuin, noggin, chordin, gremlin, follistatin, cerberus, amnionless, DAN, or the ectodomain of BMPR1A (a BMP receptor protein) or ligand binding domains from other BMP receptors.

25 41. The method according to claim 40 wherein the antagonist comprises a domain of noggin.

42. The method according to claim 41 wherein the antagonist is a human or mouse noggin.

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43. The method according to claim 42 wherein the noggin is a mouse BMP antagonist noggin comprising amino acid residues 20 to 232 of mouse noggin.

44. The method according to claim 42 wherein the noggin is in the range of 100
5 to 500 ng/ml.

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